paper copy thereof serve to place this application in a condition of adherence to the rules 37 C.F.R. § 1.821-1.825.

Claims 5 and 6 have been amended to correct an obvious clerical error.

Claims 15-28 are added herein. Generally, the added claims include subject matter regarding administration. Support is found at least on page 9, lines 1-6.

Objections

Claim 7 is objected to for having a typographical error. Claim 7 has been canceled without prejudice, rendering this objection moot.

The application is objected to for containing sequence disclosures but failing to comply with the requirements of 35 U.S.C. § 1.821 through 1.825. The concurrently submitted sequence listing and computer readable disc adequately address this objection.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-6 and 8-14 are rejected under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for localized delivery of Rad51 to a mouse and treatment effects, does not reasonably provide enablement for any method of administration and treatment of any whole organism". Applicants respectfully traverse.

The test of enablement is whether one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation, based on the disclosure and the prevailing knowledge in the field (*see* MPEP § 2164.01). Applicants submit that the present claims are enabled for individuals based on the in data provided in the specification, including but not limited to *in vivo* mouse data.

The rejected claims are directed to methods for inhibiting cell proliferation in an individual (Claims 1 & 8), inducing sensitivity to radiation in an individual (Claim 2), inhibiting the growth of a cancerous cell (Claim 4), inducing sensitivity to radiation in a

cancerous cell (Claim 6), prolonging survival of an individual (Claim 9), treating cancer in an individual (Claims 10-13) and to a kit for diagnosing and/or treating cancer (Claim 14).

The Office Action cites three obstacles to successful delivery of antisense nucleic acids to an organism: 1) penetration of the target cells; 2) withstanding enzymatic degradation; and 3) finding and binding the target while avoiding non-specific binding. Applicants submit that the primary obstacles that the use of antisense nucleic acids face are essentially the same as all nucleotides used for gene therapy. The ever-accumulating knowledge in the field, along with the teachings provided in the present application, provide substantial guidance for the skilled artisan to practice the present claims. Furthermore, the references cited by the Examiner serve to support the enablement of the present specification, rather than refute it.

Applicants first note that Flanagan (Nature Biotech. 17: 48-52 (1999)) teaches, "conventional oligonucleotides . . . can penetrate cells and demonstrate antisense effects in a variety of cell types without the aid of delivery reagents", as shown in numerous animal studies (page 51, right column). Furthermore, the specification teaches that preferred *in vivo* gene transfer techniques include transfection with viral vectors and liposome mediated transfection (page 9, lines 26-29). Such techniques are well known in the art, as will be evident from the many references cited below. For a review of the state of the art in liposome mediated nucleic acid delivery, see Templeton and Lasic, Molec. Biotech. 11:175-180 (1999). In addition, the specification also points out that short antisense nucleotides can act as inhibitors despite low intracellular concentration, and such nucleotides can be modified to enhance their uptake (page 9, lines 15-20). Moreover, the results of the *in vivo* data provided in the specification indicate that penetration takes place.

The question of withstanding enzymatic degradation is something virtually any drug must face. The skilled artisan can adjust the dosage to account for degradation. As the specification points out, these determinations may vary depending on the use envisioned and

are well within the skill of an ordinary physician (page 10, lines 26-29). The specification also notes that animal experiments provide reliable guidance for dose determination for use in humans, and interspecies scaling is based on well-accepted principles (page 10, line 29 to page 11, line 3). Moreover, the results of the *in vivo* data provided in the specification indicates that the antisense molecules are effective.

The question of finding and specifically binding the target actually has two aspects which are brought up in the Office Action. These are the ability of the nucleotide to find the target cells and the ability of the specific antisense sequence to bind the target mRNA.

With regard to the ability of the antisense nucleic acids to localize to the target of interest, Applicants point to the teachings of the specification and the general knowledge in the art. Applicants submit that while Flanagan teaches that intravenously injected nucleotides are not distributed equally among an animal's organs and tissues (page 51, right column), this is common knowledge to those of skill in the art. Flanagan goes on to state that the liver, kidney and spleen are sites of nucleotide accumulation. This fact has been taken advantage of for certain applications (*see* Ma et al., infra). The specification teaches that the nucleotides may be administered in virtually any way that is in accord with known methods, including directly into a tumor cavity or CSF. They may be administered i.v, i.p., i.c., i.m., i.o., i.a., topically, directly into a lesion or by sustained release (page 8, line 30 to page 9, line 4). The route of administration is determinable by the skilled artisan using methods generally known in the art for gene therapy applications.

The skilled artisan knows that introduction of the nucleotides in close proximity to a target increases the amount of nucleotide that will actually reach the target. Roy et al., Nature Biotechnol. 17(5):4786-479 (1999) (submitted April 17, 1998) reduced fibronectin expression in the retina by injecting antisense nucleotides into the vitreous humor of the eye. Nakamura et al., Gene Therapy 59):1165-1170 (1998) promoted angiogenesis and improved collagen deposition in an injured patellar ligament after direct injection of a liposome suspension of

nucleotides encoding platelet-derived growth factor into the ligament. McClane et al., Hum. Gene Ther. 8(6):739-746 (1997) showed a high level of gene expression in the pancreas following direct injection of adenoviral vector. Lee et al. (Ann. Thorac. Surg. 66(3):903-907 (1998)) showed that intrajugular injection of a liposome suspension of nucleic acids produced strong expression in the heart and lungs, with negligible expression in the liver and kidneys. Ma et al., Blood 90(7):2738-2746 (1997) reduced liver tumors arising from a metastatic intraocular tumor both by intraocular and intravenous injection of an adenoviral vector encoding plasminogen activator inhibitor type 1, reasoning that the activity of the nucleotide either reduced metastasis or prevented formation of new tumors after metastasis, since the size of the original tumor was not affected. These examples serve to show that determination of the route of delivery of a nucleotide for use in the present methods is standard practice in the field and dictated primarily by the nature and location of the target tissue/cells.

In the present examples, the nucleotides are injected into the cisterna magna where the tumor resides. The cells of the tumor are the primary target of the nucleotides for each of the methods claimed. This is not to say that another route of delivery would not be affective, but that this is a preferred mode of delivery for the particular examples provided, based on the common knowledge in the field.

With regard to the antisense sequences binding the target, Applicants submit that the specification provides ample support. The Office Action cites Branch, TIBS 23:45-05 (1998) to show that it is difficult to determine what antisense sequences will bind an RNA *in vivo* using *in vitro* techniques. Applicants respectfully point out that the citation refers to cell-free *in vitro* techniques. The full citation reads, "In cells, it is obviously not possible to improve specificity by raising the temperature or changing the ionic strength, . . . " (emphasis added). In contrast, the present disclosure provides "*in vitro*" examples to show how to determine the affects of antisense nucleotides in cells. Furthermore, the present specification provides *in vivo* working examples with different antisense sequences that reduced expression of both

RAD51 mRNA expression and RAD51 protein production in tumor cells (page 14, line 19 to page 15, line 19), as well as increasing their radiation sensitivity (page 15, line 20 to page 16, line 7). Working examples are also provided to show that administration of different antisense nucleotides to mice bearing tumors improved survival of the mice and increased sensitivity to radiation in tumor bearing mice (page 16, line 8 to page 17, line 1) which would otherwise have died due to proliferation of the tumor cells, causing compression of the brain and spinal cord (*see* page 17, lines 1-3).

The Office Action also cites Crystal, Science 270:404-410 (1995), to support that correlation of success in administering therapeutic nucleic acids to humans and mice is unpredictable. The cited passages (at page 409, left column) list some "surprise examples" of a lack of success in humans, despite promise from animal experiments. Applicants point out that only one type of treatment, related to tumor vaccines, is cited by Crystal. It is clear from a reading of the Crystal paper that this is the exception, not the rule. It is generally believed in the field that *in vivo* animal models are a preferred method to determine the potential of an experimental treatment. This concept is, in fact, at the foundation of modern drug discovery.

The Office Action states that the specification does not teach stability of the antisense molecules *in vivo*. Applicants reply that this is only relevant to dosage, which is readily determinable by those of skill in the art. The many examples of efficacious administration of nucleic acids cited above, along with the examples of the present disclosure, suggest that this concern is not an obstacle in the present case to provide effectiveness.

The Office Action states that the specification does not teach effective delivery to the whole organism and specificity to the target tissues. As discussed above, the route of delivery is largely dependent on the target and readily determined by the skilled artisan. The specification teaches that any of several routes of administration are possible, and the general knowledge in the art teaches that desired results are obtainable through both systemic and local administration. Of further note, the present disclosure teaches that the antisense nucleic

acids, several days after administration, were predominantly localized in the tumor tissue, not in the surrounding normal tissue (*see* page 17, lines 3-6).

The Office Action states that the specification does not teach dosage and toxicity. The specification teaches that the concentration of the therapeutically active compound in a physiologically acceptable formulation may vary from 0.1 to 100 wt.% (page 9, lines 6-8). In the examples (*see* page 14, lines 11-13), 50 ml of a formulation containing 2mM of the oligonucleotide was administered. As noted above, interspecies scaling is based on well accepted principles and is common practice in the field. Determination of effective dose and toxicity is readily determinable by the skilled artisan without undue experimentation, based on the disclosure and the general knowledge in the field.

The Office Action states that the specification does not teach entry of the therapeutic molecule into the cells and effective action therein marked by visualization of the desired treatment effects. The specification teaches several means of getting the nucleotides into a cell, including the use of viral vectors and liposomes. The list of references cited above, along with the examples in the specification, show that several efficacious means of delivering nucleotides into target cells are available and well known in the field. The specification provides working examples of efficacious activity of the antisense oligonucleotides of the present invention. Tumor cell proliferation was inhibited, resulting in increased survival of the treated individuals (Claims 1, 4 and 9-11). Survival was increased still further after radiation treatment, showing induced sensitivity to radiation in an individual (Claims 2, 5, 8 and 12). The known parallels between the activity of radiation and chemotherapeutic agents (*see* page 2, lines 15-29) supports a similar sensitization effect for chemotherapeutic agents (Claims 3, 6 and 13). Furthermore, a kit comprising a RAD51 antisense molecule is enabled by the disclosure.

The Office Action concludes that it would require undue experimentation to practice the claimed invention. Whether or not undue experimentation is required to make and use an

invention is to be determined based on several factors, including those enumerated in In re Wands,858 F.2d 731, 73, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988):

1) The breadth of the claims;

2) The nature of the invention;

3) The state of the prior art;

4) The level of skill of the ordinary artisan;

5) The level of predictability in the art;

6) The amount of direction provided by the inventor;

7) The existence of working examples; an

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims do not go beyond what is disclosed in the examples and within the reach of the ordinary skilled artisan, based on the disclosure and general knowledge in the art. The invention is in a field that is established enough to have some basic concepts, such as mode of delivery, dosage determination, extrapolation from non-human to human, confidently established. The artisan in the field of gene therapy is highly skilled. As discussed above, despite the assertions otherwise, the predictability in the field is reasonably high, particularly when *in vivo* results are provided. The specification provides ample direction, and the knowledge in the field is very extensive regarding general techniques. The specification provides working examples in cells and individuals. Furthermore, while some experimentation would be necessary, it would not be considered other than routine, given the disclosure of the specification and the general knowledge in the field (*see* MPEP 2164.06).

In In re Wands, the claims were drawn to methods of immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. The claims were rejected by the Examiner, affirmed by the Board, as requiring undue experimentation in the creation of the monoclonal antibodies. The Federal Circuit reversed, on the basis that the experimentation required was

not "undue". The steps for the creation of the monoclonal antibodies, as outlined in by the Federal Circuit, were provided:

a) an animal is immunized with the antigen of choice;
b) after a period of time, the spleen is removed;
c) the lymphocytes are separated from other spleen cells;
d) the lymphocytes are mixed with myeloma cells, and treated to fuse the cells; and
e) hybridoma cells that secrete the desired antibodies must be isolated from the "enormous mixture" of other cells, using a series of screening steps, including
    i) culturing the cells such that only hybridoma cells grow;
    ii) hybridomas are isolated and cloned, by placing single hybridoma cells in separate chambers and growing them;
    iii) the secreted antibodies from each clone are screened to see if they bind to the antigen, a step which frequently requires the screening of "hundreds" of clones.

In comparison with the *Wands* procedures, practicing the present methods is not "undue experimentation".

In light of the remarks made above, Applicants submit that Claims 1-6 and 8-14 satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. Therefore, Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102

Claim 7 is rejected under 35 U.S.C. § 102(b) as being anticipated by Taki et al., Biochem. Biophys. Res. Comm. 223:434-438 (1996). Applicants respectfully traverse.

Claim 7 has been cancelled without prejudice, rendering this rejection moot.

Applicants submit that the application is now in order for allowance and early notification of such is sincerely solicited. Please direct any calls in connection with this

application to the undersigned, Dolly A. Vance at (415) 781-1989.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

Date: 5-7-07

Dolly A. Vance
Reg. No. 39,054

Four Embarcadero Center, Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989

1. A method for inhibiting cell proliferation in an individual in vivo comprising administering to said individual a composition comprising a RAD51 antisense molecule.

2. A method for inducing sensitivity to radiation in an individual in vivo comprising administering to said individual a composition comprising a RAD51 antisense molecule.

3. A method for inducing sensitivity to a chemotherapeutic agent in an individual in vivo comprising administering to said individual a composition comprising a RAD51 antisense molecule.

4. A method for inhibiting the growth of a cancerous cell comprising administering to said cell a composition comprising a RAD51 antisense molecule.

5. (Amended) A method for inducing sensitivity to radiation in a cancerous cell comprising administering to said cell a composition comprising RAD51 antisense molecule.

6. (Amended) A method for inducing sensitivity to a chemotherapeutic agent in a cancerous cell comprising administering to said cell a composition comprising RAD51 antisense molecule.

8. The method of Claim 1 further comprising the step of administering radiation.

9. A method of prolonging the survival of an individual comprising administration to said individual a Rad51 antisense molecule.

10. A method of treating cancer in an individual comprising administration to said individual a Rad51 antisense molecule.

11. (Amended) A method according to claim 10 wherein said administration comprises localized delivery of said Rad51 antisense molecule to a cancerous or potentially cancerous site.

12. (Amended) A method according to claim [10] 11 wherein [said administration comprises localized delivery of said Rad51 antisense molecule and] said method further comprises radiation treatment [of said patient] at said site.

13. (Amended) A method according to claim [10] 11 wherein [said administration comprises localized delivery of said Rad51 antisense molecule and] said method further comprises chemotherapeutic treatment of said patient.

14. A kit for diagnosing and/or treating cancer comprising a Rad51 antisense molecule.

15. The method of Claim 1, wherein said administering is locally to a site wherein said cell proliferation is to be inhibited.

16. The method of Claim 15, wherein said administering is by injection.

17. The method of Claim 15, wherein said site is to a tumor.

18. The method of Claim 2, wherein said administering is locally to a site wherein said sensitivity is to be induced.

19. The method of Claim 18, wherein said administering is by injection.

20. The method of Claim 18, wherein said site is to a tumor.

21. The method of Claim 3, wherein said administering is locally to a site wherein said sensitivity is to be induced.

22. The method of Claim 21, wherein said administering is by injection.

23. The method of Claim 21, wherein said site is to a tumor.

24. The method of Claim 9, wherein said individual is in need of inhibition of cell proliferation, and wherein said administering is locally to a site wherein cell proliferation is to be inhibited.

25. The method of Claim 24, wherein said administering is by injection.

26. The method of Claim 24, wherein said site is to a tumor.

27. The method of Claim 11, wherein said site has a tumor or wherein a tumor has been removed.

28. The method of Claim 11, wherein said administering is by injection to a tumor.